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Development of Charcot Neuroarthropathy in Diabetic Patients who Received Kidney or Kidney-Pancreas Transplants

Michael L. Anthony, DPM[1], Kimberly S. Cravey, DPM[2], Said A. Atway, DPM, FACFAS[3]

[1] Assistant Professor, Podiatric Medicine and Surgery Residency Program, The Ohio State University Wexner Medical Center, Columbus, OH
[2] Resident, Podiatric Medicine and Surgery Residency Program, The Ohio State University Wexner Medical Center, Columbus, OH
[3] Assistant Professor, Podiatric Medicine and Surgery Residency Program, The Ohio State University Wexner Medical Center, Columbus, OH

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ABSTRACT

Only a small percentage of the general diabetic population develops Charcot neuroarthropathy. Charcot arthropathy greatly increases the risk of foot complications. At our academic institution, there appeared to be an increased incidence of Charcot arthropathy in transplant patients. We hypothesized that Charcot neuroarthropathy incidence is higher in the diabetic patients who had received kidney or kidney-pancreas transplants. The charts of 1000 patients were reviewed from January 2000 to January 2011. Four hundred and eighty-seven patients were included in the study. Of these diabetic patients, 249 had received a kidney transplant and 238 a kidney-pancreas transplant. The data were analyzed for the incidence of Charcot in each group. Other risk factors and sequelae were also evaluated and analyzed. The incidence of Charcot development in the diabetic patients who had a kidney-pancreas transplant was 18.4%, 44 of 238 patients. This was significantly higher than the incidence in kidney transplant patients, which was 11.2%, 28 of 249 patients ($p < .05$). Peripheral arterial disease was a statistically significant independent risk factor for developing ulceration, osteomyelitis, and subsequent amputation. Type 1 diabetic patients developed Charcot at a higher rate that was also statistically significant compared with type 2 diabetic patients. In our study, diabetic patients who had undergone kidney-pancreas transplants were associated with higher risk for development of Charcot neuroarthropathy than kidney transplants alone. The incidence of Charcot development in both these transplant groups was also much higher than in the general diabetic population. This is of particular interest to clinicians and surgeons as both transplant groups were found to be high risk for subsequent foot ulceration, infection, and amputation.

Charcot neuroarthropathy is a devastating, progressive joint destructive disease process with significant sequelae, leading to foot deformity, ulceration, infection, and, in many cases, amputation. The pathophysiology is multifactorial and not completely understood. There is still much debate and discussion regarding the subject, including diagnosis, classification, and treatment (1–4). It is most commonly found in patients with diabetes mellitus with peripheral neuropathy, although it has been found in patients with a multitude of other disease processes that cause neuropathy (1). The incidence of diabetes continues to rise and the World Health Organization estimated a 9% prevalence of diabetes among adults in the world as of 2014 (5). The incidence and prevalence of Charcot neuroarthropathy in diabetics has been reported to be as low as <0.1% to as high as 7.5% of the general diabetic population. Multiple epidemiological studies in the United Kingdom have shown the incidence of Charcot never higher than 0.4% of the general diabetic population (6). The Incidence of peripheral neuropathy in the diabetic population is estimated to be from 9% to 32%. One report shows high-risk patients with neuropathy to have a 13% prevalence of Charcot (7). Some of those numbers may be underreported because Charcot remains difficult to diagnose, and there is no standard diagnostic criteria (3). Delay in diagnosis adversely affects quality of life and functional outcome, as the complications associated with Charcot foot can be devastating (8).

Because it is a rare disease and not all aspects of the disease are fully understood, there is much to be studied. Recently, there has been some literature linking solid organ transplants to development of Charcot arthropathy (9–12). The working hypothesis is that there is an increased incidence of Charcot neuroarthropathy in diabetics who had kidney or kidney-pancreas transplants. This is important to recognize in this immunocompromised group because the complications and sequelae may be magnified.

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Address correspondence to Kimberly S. Cravey, DPM, The Ohio State University Wexner Medical Center, Department of Orthopaedics, Bradwell Crossing, Grove City, OH 43123

E-mail address: kcravey@kent.edu (K.S. Cravey).

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Table 1
The association between developing Charcot and demographic variables of sex, age, or race

	Male	Female	Age ≤57	Age >57	Caucasian	African American
Charcot	43 (15%)	28 (14%)	35 (13.7%)	36 (15.5%)	58 (15.3%)	13 (12.3%)
Non-Charcot	244 (85%)	172 (86%)	220 (86.3%)	196 (84.5%)	320 (84.7%)	93 (87.7%)
Total	287	200	255	232	378	106
chi-square	0.1585		0.20296		0.75565	
p	.6905		.65233		.38469	

The median age for our data was 57 years; these data were divided into 2 groups (older or younger than the median age). Three patients were another race besides Caucasian and African American. These patients were not represented in this table. Demographics N = 487.

Materials and Methods

This is a retrospective case series evaluating diabetic patients who had also undergone kidney or kidney-pancreas transplants. At our academic institution, 1000 patient charts were reviewed from January 2000 to January 2011, after IRB approval was obtained. The charts were identified using International Classification of Diseases-9 codes for solid-organ transplants, specifically for kidney and kidney-pancreas transplants. Patients were included in the study if they had been diagnosed with diabetes and had received a kidney transplant (249 patients) or a kidney-pancreas transplant (238 patients). A follow-up period >2 years after transplant surgery was also required for inclusion. Four hundred and eighty-seven patients met all inclusion criteria. The majority of the patients were male and Caucasian, with a median age of 57 (Table 1). A total of 513 patients of the original 1000 charts identified did not meet the inclusion criteria. There were no further exclusion criteria for patients meeting these inclusion requirements. Charts were reviewed for age, sex, race, history of ulceration, ulcer location, amputation, length of follow-up, type of diabetes mellitus, smoking status, glycemic control (HgbA1C level), peripheral arterial disease (PAD), presence of neuropathy, and whether surgical reconstruction was performed. Type 1 diabetic patients were distinguished from type 2 diabetic patients per diagnosis listed in the patient's chart. Radiographs were not evaluated to determine location of Charcot foot deformity for each patient. These data were analyzed to help identify potential associated risks factors in the development of Charcot neuroarthropathy in this specific patient population.

Chi-squared 2-sample testing was performed between the variables identified, and *p* values were calculated. We included 95% confidence intervals (CIs) for all variables with statistical significance defined at the 5% ($p = .05$). Finally, logistic regression was performed for each of the potential complications of osteomyelitis, ulceration, and amputation. This was based on the variables of PAD, Hgb A1c ≥8.0, smoking, age, and diabetes type. Median age was determined to be 57 years and our data were divided to evaluate "older" and "younger" subgroups as defined as >57 years and <57 years of age, respectively. Furthermore, HgbA1c ≥8.0 was defined as uncontrolled diabetes for the purpose of this study and patients were therefore divided into 2 groups accordingly.

Results

A total of 72 (14.8%) patients developed Charcot arthropathy of 487 patients in the study. Of those 487 patients, 277 (56.9%) had neuropathy. As expected, all 72 of the patients who developed Charcot also had neuropathy. Demographics were not significant variables for developing Charcot (Table 1). In the diabetic patients who had a kidney-pancreas transplant, 44 (18.4%) of 238 ($p = .024$, 95% CI) developed Charcot. Of the diabetic patients who had a kidney transplant alone, 28 (11%) of 249 developed Charcot. Having a kidney-pancreas transplant was statistically significant versus kidney transplant for developing Charcot (Table 2). When the 277 diabetic peripheral neuropathy patients were isolated, the incidence of developing Charcot in the kidney-pancreas group was 31.4% ($p = .037$, 95% CI), which was statistically significant compared with the kidney transplant group, which had an incidence of 20.4% (Table 2).

Table 2
The percentage of patients with a kidney-pancreas transplant who develop Charcot is significantly higher than those with kidney transplant

	All Patients (N = 487)		Neuropathic Patients (n = 277)	
	Kidney	Kidney-Pancreas	Kidney	Kidney-Pancreas
Charcot	28	44	28	44
Non-Charcot	221	194	109	96
Total	249	238	137	140
Incidence of Charcot	11.2%	18.4%	20.4%	31.4%
Chi-square	5.066		4.34796	
p < .05	.024395		00370532	

The average time to developing Charcot was 6.4 ± 4.8 years in the kidney-pancreas transplant group and 7.1 ± 5.2 years in the kidney transplant group alone. Only 1% of the total patients developed Charcot within a year of transplant. The average HgbA1c level was 6.8 in the kidney-pancreas group and 8.9 in the kidney group. HgbA1c levels, presence of PAD, and smoking were not statistically significant variables for developing Charcot (Table 3). Fifty-four (20%) of 270 type 1 diabetic patients developed Charcot arthropathy compared with 18 (8.3%) of 217 type 2 diabetic patients. Therefore, type 1 diabetic patients developed Charcot arthropathy at a statistically significant higher rate than type 2 diabetic patients ($p = .0003$, 95% CI) (Table 4).

Patients developing Charcot had statistically significant higher risk of developing ulcer, osteomyelitis, and amputation ($p < .05$, 95% CI) (Table 5). In total, there were 19 (26%) of 72 Charcot patients who subsequently underwent surgical reconstruction. Of those 19 patients, 12 (63%) acquired pedal ulceration and 6 (32%) ultimately required some level of lower extremity amputation. The incidence of ulceration, osteomyelitis, and amputation in patients with Charcot was found to nearly double that of the total patient group (Table 6).

In all 487 patients, logistic regression showed that the odds for developing ulceration, osteomyelitis, and amputation were much higher if the patient also had PAD. Odds of developing complications were high in both patient groups of PAD: those with and without Charcot (Table 7). Based on the results of this study, the

Table 3
The association between developing Charcot and smoking, HgbA1c levels ≥8, or presence of PAD

	Smoker	Nonsmoker	A1c <8	A1c ≥8	PAD, No	PAD, Yes
Charcot	20 (11.2%)	52 (16.7%)	33 (12.9%)	21 (13.7%)	47 (18%)	25 (19.4%)
Non-Charcot	159 (88.8%)	259 (83.3%)	223 (87.1%)	132 (86.3%)	214 (82%)	104 (80.6%)
Chi-square	2.78887		0.05824		0.1079	
p	.0949		.800929		.74245	

Table 4
Type 1 DM patients develop Charcot significantly more than type 2 diabetic patients

	Type 1 DM		Type 2 DM
Charcot	54 (20%)		18 (8.3%)
Non-Charcot	216 (80%)		199 (91.7%)
Total	270		217
Chi-square		12.9818	
p		.0003145	

Abbreviation: DM, diabetes mellitus.

incidence of developing Charcot in diabetics with kidney-pancreas transplant was 18% and 11% in diabetic kidney transplants. In those diabetic patients who were diagnosed with peripheral neuropathy, the incidence of Charcot development increased to 20% from 11% in the kidney transplant study population. The incidence of Charcot development in the kidney-pancreas group rose to 31.4% from 18% in the study group.

Discussion

Although Charcot neuroarthropathy is a familiar pathologic process for those who care for the diabetic foot, not all is understood about this disease process and there is still much to be learned. The Charcot foot has been documented to occur most commonly as a consequence of diabetic peripheral neuropathy. In addition to causing loss of pain perception, peripheral neuropathy can also cause impaired microcirculation, impaired fluid hemostasis, diminished energy metabolism, and altered the local immune response (13).

Although the pathophysiology of Charcot is still not fully understood, the prevailing belief is that it is multifactorial, mediated by hyperemia and undetected repetitive trauma (3,5,14,15). Jeffcoate et al. has proposed that in acute Charcot an initial traumatic insult triggers the inflammatory cascade and the RANKL NF-β pathway, which leads to osteolysis and fracture (2,14). This bony destruction is thought to be directly if not indirectly responsible for the progressive fracture dislocation. This collapse of the bones and joints leads to bony deformity, most commonly located at the plantar midfoot and the ankle (16). This progressive deformity places these patients at higher risk for ulceration, infection, and ultimately amputation, especially if those ulcerations are inadequately offloaded in corrective shoes or braces.

In our study, the same conclusions can be drawn regarding Charcot patients being at high risk of foot complications. Forty-two percent of the diabetic transplant patients and 80% of the Charcot patients developed an ulcer. Among all diabetic patients, it has been estimated that only approximately 15% will develop an ulcer in their lifetime (17). Additionally, 33% of all our study patients acquired osteomyelitis compared with 64% of the Charcot patients. Thirty-one percent of all patients underwent some form of amputation compared with 61% of the Charcot group.

Conservative treatment is aimed at immobilization and offloading the pressure areas or ulcerations, usually with orthotics, custom shoes, walking boots, or total contact casting (7). The goal of surgical treatment is to restore a plantigrade foot to offload and heal wounds and prevent potential future deformity, ulcerations, and infections. There is no standardized treatment algorithm to help clinicians and surgeons in deciding which patients will benefit from conservative versus surgical treatment. The presence of high-risk factors such as ulceration, bony deformity, osteopenia, obesity, and immune-compromised illness, led Pinzur et al. to propose more conservative treatment in Charcot patients (18).

There are some proposed reasons why diabetic transplant patients might develop Charcot arthropathy more commonly than the general diabetic patient. One of the common comorbidities in diabetic patients is nephropathy, which leads to end-stage renal disease (ESRD) and need for dialysis. Those patients who have ESRD and are on dialysis have been shown to have higher rates of foot disease, and have been shown to have worse neuropathy (19). Those in need of kidney transplant suffer increased chronicity and severity of kidney disease, placing them at even higher risk. Eggers et al. found that diabetic patients with ESRD had 10 times the risk for lower extremity amputation than the general diabetic population as a whole (20). Kidney transplantation is the standard and principal treatment option for those with ESRD (20,21). Type 1 diabetic patients with kidney disease are potential candidates for spontaneous kidney-pancreas transplant. Long-term survival studies have shown that in type 1 diabetic patients, a successful kidney-pancreas transplant is life enhancing and lifesaving when compared to kidney transplant alone, as the pancreas transplant improves the quality of life and prevents the progression of secondary complications of diabetes (21).

The orthopedic and transplant literature has consistently shown a high rate of osteoporosis after renal transplants (22). There is a 50% prevalence of osteoporosis, and 4 times' higher risk of fractures after renal transplant. The pathophysiology is related to abnormal bone metabolism related to parathyroid hormone, calcium, vitamin D levels, glucocorticoid use after transplant, and existing metabolic bone disease (23). Most of the patients will develop the bone disease in the first year after surgery, but it has been shown to continue on years after the

Table 6
The percentage of Charcot patients who had ulcer, osteomyelitis, or amputation was double that of the total patient group

	Ulcer	Osteomyelitis	Amputation
All diabetic patients (N = 487)	42%	33%	31%
Charcot patients (n = 72)	80%	64%	61%

Table 7
The odds of developing an ulcer in a patient with Charcot are 9.2 times higher if he or she had PAD than if there was no PAD

	Ulcer	Osteomyelitis	Amputation
Charcot	9.2	29.6	34.4
No Charcot	12.7	17.7	17.9

Abbreviation: PAD, peripheral artery disease.

Table 5
The risk of developing ulcer, osteomyelitis, and amputation is significantly higher in Charcot patients

	Ulcer	No Ulcer	Osteomyelitis	No Osteomyelitis	Amputation	No Amputation
Charcot	58 (28.2%)	14 (5%)	46 (28.8%)	26 (8%)	44 (29.3%)	28 (8.3%)
Non-Charcot	148 (72.8%)	267 (95%)	114 (71.3%)	301 (92%)	106 (70.7%)	309 (91.7%)
Total	206	281	160	327	150	337
Chi-square	50.772		49		36.333	
p	<.0001		<.0001		<.0001	

Osteomyelitis was defined by chart diagnosis and review of chart notes.

surgery as well. Only 1% of the patients in the present study developed Charcot within a year of the surgery.

The development of Charcot in this very narrow patient population has been reported by a few other authors recently. There are a limited number of studies that have investigated the correlation between renal-pancreas transplants and Charcot development. Rangel et al. in 2012 performed a retrospective review of 130 patients who had a kidney-pancreas transplant. It was noted that 4.6% of patients went on to develop de novo Charcot within the first year after surgery. His study found that glucocorticoids are the main risk factor for this development because the immunosuppression leads to metabolic bone loss and fracture (5). Matricali et al. in 2007 did a retrospective study of 66 type 1 diabetic patients over 12 years who had kidney-pancreas transplant surgery for ESRD. They found that 8 (12%) of the 66 type 1 diabetic patients developed acute Charcot and that 4 of those occurred within a year of the transplant surgery (9). Del Vecchio et al., in 2013, published 2 case reports of patients who developed rather quick onset of Charcot neuroneuroarthropathy after kidney-pancreas transplantation (12). Nehring's study showed that in diabetic patients who have Charcot, the risks factors are male gender, increased age, duration of diabetes, height, body weight, and hip circumference; however, this study did not address any transplant patients (24). Valabhji discussed that there is a high association of diabetic patients with impaired renal function and ESRD that develop Charcot neuroarthropathy (11). It was unclear exactly what the relationship is, but that it could be due to associated microvascular complications of nephropathy, combined with the peripheral neuropathy. In our study, PAD had a dramatic influence on the patient population and was an independent risk factor for causing ulcer, infection, and amputation in the Charcot and non-Charcot patients.

Another potential cause of this relationship was altered bone metabolism from renal disease, which can lead to a poorer metabolic state that may allow for the development of the Charcot process (6). Boucek's study looked to determine if by doing a kidney-pancreas transplant on type 1 diabetic patients, the nerve function would be improved. His study showed that the transplant does not lead to regeneration of the nerve fibers and did not eliminate risks connected with diabetic neuropathy (25).

Increased HgbA1c was not found to be an independent risk factor for developing Charcot neuroarthropathy in our study population, despite increased risk of wound infection and postsurgical complications associated with HbA1c >8.0 (26–28). Perhaps further evaluation of HbA1c and its relationship to diabetic Charcot foot complications may be beneficial in future research.

To our knowledge, this is the largest retrospective review of Charcot foot development in diabetic solid organ transplant recipients. At the host academic medical center, there are a large number of transplant surgery procedures performed each year. These patients are commonly seen in consultation for diabetic foot ulcerations, Charcot foot deformities, and foot infections. Anecdotal observations were made that a large portion of transplant patients seemed to have Charcot deformities, and this prompted the scientific inquiry.

This retrospective chart review does present some inherent limitations that are recognized by the authors. The first is that all data were gathered from electronic charts via International Classification of Diseases-9 codes, overall making the results less reliable. The diagnostic codes for transplant, diabetes, and Charcot were documented from any point in the patient's medical record, including historical documentation only. These data are not as reliable for direct comparisons of someone who had a kidney transplant many years ago with other patients who had acute Charcot development right after transplant surgery, for example. Some of the patients had multiple kidney transplant surgeries, and some were even years apart. Other patients had both isolated kidney transplants, with an isolated pancreas transplant performed years later, and vice versa. The statistical data were evaluated to include all those with simultaneous kidney-pancreas transplants and those who had staggered procedures; this did not change the statistical significance. Additionally, there were a small number of patients who had isolated pancreas transplants; the statistical significance was not changed when their data were removed from the calculations. Because some patients had transplant surgery 20 years ago, the timing of Charcot diagnosis might not be as accurate as if this were a prospective study. Again, the diagnosis of Charcot has traditionally been missed or delayed because of a lack of specific training in this subject area across different specialties and a lack of standardized diagnostic criteria. This may be why the time of Charcot onset in this study was much longer than the other studies referenced.

Additionally, glucocorticoid and immunosuppresive medications were not evaluated to determine the causal effect on Charcot development, as was discussed in some of the studies mentioned. It would have been very difficult to find medication regimens only through chart review and without talking to patients. The findings from Rangel's study in 2012 that glucocorticoids played a role in Charcot development could have further validated, but this was too difficult a task in a long-term retrospective study. In this field of Charcot research, this would would be a good approach for potential future prospective studies.

Third, the offloading modalities and other forms of conservative treatment were not factored into the data regarding ulceration, osteomyelitis, and amputations. This skewed the information about wound and amputation percentages based only on 1 risk factor of Charcot development. The weightbearing and activity levels of the patients were not evaluated, which could have better identified patients who have higher plantar foot pressures and subsequent increased risk of ulceration and amputation. It is unclear if these patients were being followed by a foot sugeon at any point.

In conclusion, diabetic patients generally are at low risk for developing Charcot arthropathy. Patients with neuropathy have been shown to be more likely to develop Charcot neuroarthropathy and kidney-pancreas or isolated kidney transplant patients seem to be at further increased risk. Clinicians and surgeons can use this information to better educate their patients in attempts to prevent development of these high-risk comorbid conditions, which increases their risk of complication and limb loss. Clinicians and surgeons who care for diabetics with transplants might also raise their index of suspicion of any foot problems, especially Charcot. This information provides another small piece to the complex puzzle of Charcot arthropathy.

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